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PATENT
Attorney Docket No. 15270L-008930US
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. 7805
Dale B. Schenk et al.	Examiner: Michelle S. Horning
Application No.: 10/698,099	Technology Center/Art Unit: 1648
Filed: October 31, 2003	APPELLANT'S BRIEF UNDER 37 CFR §41.37
For: PREVENTION AND TREATMENT OF SYNUCLEINOPATHIC DISEASE	

Mail Stop Appeal Brief
Commissioner for Patents
P.O. Box 1450
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Commissioner:

Further to the Notice of Appeal filed October 9, 2009 in the above-referenced application, Appellant submits this Brief on Appeal.

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1. REAL PARTY IN INTEREST

The application is assigned to Elan Pharmaceuticals, Inc. and the Regents of the University of California

2. RELATED APPEALS AND INTERFERENCES

An Appeal Board has rendered a decision on appeal and a decision on request for rehearing in Appeal Number 2006-3375 for related case, US Application No. 09/723,765. An appeal is pending in related case 10/777,792. Two appeal briefs have been filed in related case 10/699,517, but on each occasion the Examiner reopened prosecution. This case has now been allowed. However, the issues in the present case are not closely analogous to the issues in the related cases listed.

3. STATUS OF CLAIMS

Claims 1, 3-6 and 54-55 are pending and appealed. Claims 2, 7-13 and 14-53 are cancelled.

4. STATUS OF AMENDMENTS

An amendment after final is being filed herewith cancelling claims 9-13.

5. SUMMARY OF CLAIMED SUBJECT MATTER

One independent claim, claim 1, is on appeal. Claim 1 is directed to a composition comprising an agent effective to elicit an immunogenic response to alpha-synuclein and an adjuvant that is pharmaceutically acceptable for human administration (see, e.g., paragraph 154). The adjuvant is selected from the group consisting of QS21, monophosphoryl lipid, alum, CpG, GM-CSF and M-CSF (see paragraphs 150-152). The agent is alpha-synuclein or an immunogenic fragment thereof (see paragraph 56). The invention provides a working example showing that immunization with alpha-synuclein and an adjuvant results in a clearing response against synuclein deposits in a transgenic mouse model of synucleinopathic disease (pp. 59-60). Although the adjuvant used in these experiments was not a pharmaceutically acceptable

adjuvant for human administration (because the experiments were performed on a mouse), the experiment demonstrates proof of principle that immunization with alpha-synuclein and an adjuvant has useful activity in synucleinopathic disease and provides a foundation for the above-described claim in which alpha synuclein or an adjuvant is combined with a pharmaceutically acceptable adjuvant for human administration.

Claim 54, which depends from claim 1, specifies that the composition is made under good manufacturing practice conditions (see paragraph 56).

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether claims 1, 3, 6, 9-13 and 54-55 would have been obvious under 35 U.S.C. 103(a) over "Ueda," Proc. Natl. Acad. Sci. USA 90, 11282-11286 (1993) in view of US Patent Nos. 6,416,947 ('947), 5,583,112 ('112) and 6,172,122 ('122).

7. ARGUMENT

7.1 The Examiner's rationale

The Examiner's rationale is stated in most detail in the penultimate office action, dated October 24, 2008. Ueda is cited regarding using NAC fragments conjugated to KLH to make polyclonal sera in rabbits (penultimate office action at p. 3, 2nd paragraph). The '947 patent is cited regarding use of lipid A or aluminum hydroxide as adjuvants and as teaching that making a vaccine under GMP conditions results in less potency (penultimate office action at p. 3, third paragraph) . The '112 patent is cited regarding use of QS21 as an adjuvant (penultimate office action at p. 4, first full paragraph). The '122 patent is cited regarding the goals of good manufacturing practice in avoiding adulteration (penultimate office action at p. 4, first full paragraph). The Examiner alleges that it would have been obvious to combine the references to increase antibody titers. The Examiner further alleges it would have been obvious to use GMP conditions to obtain a desired purity and that a loss of potency associated with GMP conditions would have further motivated use of an adjuvant (penultimate office action at p. 5, second paragraph). A similar rejection was made and withdrawn earlier in prosecution in which Yoshimoto, *Proc. Natl. Acad. Sci. USA* 92:9141-9145 (1995) or Wakabayashi, *Neuroscience Letters,* 239(1):45-48 (1997) was cited as using alpha synuclein fragments to raise polyclonal

sera and a secondary reference Cleland, *J. Pharm. Sci.,* 85, 22-28 (1996) was cited as teaching a stable preparation of QS21 in the context of a HIV vaccine (office action of November 15, 2006).

7. 2 Summary of the Cited Art

Ueda discusses making polyclonal sera to alpha-synuclein fragments. This discussion occurs in the Material and Method section (p. 11282, second column last paragraph) and is extremely brief lacking details of the immunization protocol and use of adjuvant. However, further details can reasonably be inferred by reviewing other papers from the same research group with overlapping authorship, in particular Yoshimoto and Wakabayashi, which were cited in the office action of November 15, 2006. These references also describe making polyclonal sera to alpha synuclein fragment. Indeed, the nine amino acid NAC peptide "X1" described in Yoshimoto at p. 9141, second column, 3rd paragraph appears to be the very same peptide as the nine amino acid NAC peptide "X1" described at p. 11282, second column, third paragraph of Ueda. Thus, it appears that Ueda is in fact describing preparation of the same polyclonal antibody preparation as Yoshimoto. Like Ueda, Yoshimoto and Wakabayashi are silent as to which adjuvant was used. However, in the case of Yoshimoto and Wakabayashi, it can be conclusively determined that the adjuvant was Freund's adjuvant by tracing back through the cited references to Iwai et al., *Neuron,* 14:467-475 (1995) (reference 21 in the Yoshimoto paper). Iwai et al. indicate that polyclonal sera was generated using Freund's adjuvant (complete Freund's adjuvant for first inoculation and incomplete Freund's adjuvant for subsequent inoculations). According to Harlow & Lane, *Antibodies: A Laboratory Manual* (CSHL 1988)) at p. 98 Freund's adjuvant is the most commonly used for immunization laboratory animals but is too toxic for use in humans.[1]

To conclude, although Ueda does not explicitly describe use of an adjuvant, it can reasonably be concluded from other references from the same research group discussing the

[1] Purer forms of incomplete Freund's adjuvant, for example, sold under the trade name of Montanide can be used for administration to humans (see, e.g., Chang, *Advanced Drug Delivery Reviews* 32:173-186 (1988). However, there is no indication that Iwai et al. used anything other than a standard laboratory grade.

same procedure for generating polyclonal antibodies if not the very same preparation of polyclonal antibodies, that Ueda also used Freund's adjuvant.

The '947 patent mainly discusses an adjuvant termed a poloxamer. The potency of the adjuvant is compared with Freund's adjuvant, alum, Quil A (of which QS-21 is a component) and a Ribi oil and water formulation. Both the poloxamer and Freund's adjuvant were characterized as "potent adjuvants" inducing "high titered antibody responses" (col. 20, lines 1-8). However, the poloxamer was found to be more immunogenic than alum and Quil A and possibly more immunogenic than Ribi O/W (col. 20, lines 19-22). The '112 patent discusses use of saposins, such as Quil A, as adjuvants in vaccines and indicates they are preferably used for administration to a human (see col. 8, line 12-16). Although the Examiner cites the '947 patent as disclosing "it is generally expected that a vaccine prepared in accordance with Good Manufacturing Practices ("CMP") prescribed by the U.S. Food and Drug Administration will be less potent than one prepared otherwise" (penultimate office action at p. 3), appellant does not find such disclosure in the '947 patent.

The '122 patent discloses that GMP regulations specify a means to assure a clean product which is of purity suitable for its intended use. However, the intended uses of the compositions described in the '122 patent include foods as well as pharmaceuticals (see e.g., col. 1, lines 10-12).

7.3 The Cited Art Distinguished

The case of obviousness as understood by appellant is that it would have been obvious to combine Ueda, disclosing an alpha synuclein fragment, with the '947 or '112 patents disclosing adjuvants suitable for human administration, to increase antibody titers, and further, it would have been obvious to use GMP conditions to obtain a desired purity and that a loss of potency associated with GMP conditions would have further motivated use of an adjuvant (penultimate office action at p. 5, second paragraph). Appellant disagrees with this combination of the references because the proposed combination did not represent the common-sense approach of the artisan at the relevant time but rather an impermissible hindsight reconstruction,

and because the presently claimed compositions are associated with an unexpected gain of function relative to the art.

Although motivation is not applied as a rigid formula denying recourse to common sense, it can still be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. *KSR International Co. v. Teleflex Inc.*, 550 US 398, 418, 82 USPQ2d 1385, 1396 (U.S. 2007). Furthermore, a factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning. *Id.* at 421. 82 USPQ2d 1385, 1397 (U.S. 2007).

Here, the asserted combination of references rests at least in part on the incorrect premise that Ueda was not using any adjuvant, and that it would have been obvious to include an adjuvant to increase antibody titer. This assumption is almost certainly incorrect. As discussed above, it is more likely that Ueda used complete Freund's adjuvant followed by incomplete Freund's adjuvant as in the other reports from the same group noted above (Yoshimoto, Wakabayashi and Iwai).

Absent the incorrect assumption that Ueda used no adjuvant, there would have been no reason to think that alum or lipid A would increase antibody titer beyond what was already being obtained. There would also have been no reason to think that alum or lipid A would compensate for an alleged loss of potency caused by manufacture under GMP conditions (assuming such a loss were to occur, which in appellant's submission has not been established). . The '697 patent does not provide any evidence that alum and lipid A are more potent that its polyoxamer or Freund's adjuvant and in fact suggests the reverse is the case (as summarized above). Accordingly, a skilled person following common sense would not have replaced Freund's adjuvant with alum or lipid A due to concerns regarding inadequate potency of Freund's adjuvant.

With respect to claim 54, the case of obviousness assumes that laboratory researchers would voluntarily make a polyclonal antibody as a research reagent under GMP conditions. Such assumption is respectfully submitted to be implausible. The considerations facing drug manufacturers, to whom GMP regulations are directed, and laboratory researchers

are entirely different. Drug manufacturers make large quantities of a drug for a therapeutic use. Laboratory researchers make relatively small quantities of a polyclonal antibody for research use; moreover, the animal used in the experiment is usually sacrificed at the end of the experiment. The degree of purity imposed on manufacturers of drugs to ensure safety of human patients and consequent GMP procedures to achieve it would have appeared an unnecessary and onerous burden to a laboratory researcher and would not have been self-imposed. No evidence has been provided that GMP conditions have ever been used in laboratory research.

Although the Examiner alleges that obviousness is necessarily a hindsight reconstruction (final office action at p. 5, first paragraph), there are several factors here that suggest the reconstruction is not based on a realistic assessment of the mindset of the artisan at the relevant time. The case of obviousness simply assumes that Ueda did not use an adjuvant, whereas closer examination of the circumstances indicates it is more likely that he used complete and incomplete Freund's adjuvant as did other references describing preparation of the same or similar polyclonal sera from the same research group.. The case of obviousness assumes that the skilled person would use alum or lipid A to compensate for a loss of potency from using GMP conditions, without evidence that such a loss of potency would occur and, when in any event, it is likely that Ueda was already using a more potent adjuvant (i.e., Freund's adjuvant). With respect to claim 54, the case of obviousness assumes a laboratory researcher would self-impose GMP conditions without any evidence that such conditions have ever been employed by any laboratory worker. In view of all of these assumptions, the proposed case of obviousness lacks adequate safeguards against impermissible hindsight.

Finally, the present compositions are associated with an unexpected result or gain of function relative to the art. The unexpected gain of function is that the claimed pharmaceutical compositions can be administered to humans to treat Parkinson's disease as distinct from being used to generate a laboratory reagent for basic research (see summary of invention). The unexpected nature of the result lies not in the discovery that the adjuvants of the present claims are suitable for human administration, but rather in the insight that alpha-synuclein could have a distinct therapeutic role from merely being a laboratory reagent if

combined with an otherwise art-known means (i.e., a pharmaceutically acceptable adjuvant suitable for administration to humans).

Most of appellant's above remarks were presented by way of response to the penultimate office action. The Examiner has in turn responded to appellant's remarks in the final rejection of June 10, 2009. Appellant now responds to address the Examiner's remarks.

The Examiner alleges that it is improper for appellant to consider other papers from the same group as Ueda to "read in" a limitation of Freund's adjuvant into Ueda's approach to generating antibodies (final office action at p. 3). Appellant disagrees. The other papers from the same group (some of which were cited by the Examiner earlier in prosecution) are used to illustrate how a skilled person would interpret Ueda's description of antibody generation. Specifically, the other papers illustrate that Ueda's research group used Freund's adjuvant in the same or similar work elsewhere leading to the likely conclusion that Freund's adjuvant is not mentioned in the cited paper only for purposes of brevity. Conversely, arbitrarily selecting one reference by Ueda's group, which probably for no reason other than brevity does not mention Freund's adjuvant, to the exclusion of other papers that do disclose Freund's adjuvant appears to be an artificial approach not in keeping with the common sense of an artisan at the relevant time.

The Examiner also alleges that whether Ueda used an adjuvant or not does not by itself determine obviousness or lack thereof (final office action at p.3). Appellant agrees to the extent that even if Ueda had not used an adjuvant at all, it still would not have been obvious to combine alpha synuclein with an adjuvant suitable for a human administration for the research purposes contemplated by Ueda. Nevertheless, the fact that Ueda would be understood to have used Freund's adjuvant and the case of obviousness therefore requires replacing the most common adjuvant for laboratory animal work (see Harlow & Lane, discussed above) with an adjuvant suitable for human administration focuses in sharper relief the departure from the common sense approach of the artisan required by the asserted case of obviousness.

In the paragraph bridging pp. 3-4 of the final office action, the Examiner acknowledges appellant's remark that the '697 patent suggests that alum and Quil A are less rather than more potent adjuvants than Freund's adjuvant, but says it is not clear why alum and Quil A need to be more potent that Freund's adjuvant. In reply, the Examiner proposed

increased potency as a basis for inclusion of alum or Quil A (penultimate office action at p. 5, second paragraph). Without evidence that Quil A or alum were at more potent or at the very least as potent as Freund's adjuvant, common sense would dictate that the artisan would continue to use Freund's adjuvant, the most common adjuvant used in animal work.

In the same paragraph of the final office action, the office action cited MPEP 2123 for the proposition that even non-preferred embodiments are to be considered in making determinations of obviousness (final office action at p. 5, last paragraph). Although MPEP § 2123(I) provides that non-preferred embodiments constitute prior art, it does not say that the characterization of one element of a claim as non-preferred is determinative that the claim as a whole is obvious. The cases cited in MPEP § 2123(I) involve unrelated facts and circumstances to the present. Two of the cases (*Upsher-Smith Labs. v. Pamlab, LLC*, 412 F.3d 1319, 75 USPQ2d 1213 (Fed. Cir. 2005); and *Celeritas Technologies Ltd. v. Rockwell International Corp.*, 150 F.3d 1354, 47 USPQ2d 1516 (Fed. Cir. 1998)) involved anticipation, the issue being whether a single reference disclosing an embodiment of an invention characterized as non-preferred still anticipated. The third case (*Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied,* 493 U.S. 975 (1989)) involved obviousness based on a single reference. The invention in *Merck* was a combination of a first component and a second component, both of which were known drugs. The prior art reference disclosed that a genus of 10 drugs (comprising the first component) could be combined with another genus of 120 drugs (comprising the second component) for the identical purpose as claimed. Neither the first component, nor the second component, however, was highlighted as a preferred embodiment in the prior art reference. Against this background, the court stated "all disclosures of the prior art, including unpreferred embodiments, must be considered." *Id.* at 807.

The present facts and circumstances are distinguishable from those in *Merck*. *Merck* involved the combination of two drugs from two lists of drugs, the combination having the same use as the individual drugs Here, the case of alleged obviousness in part on one reference (Ueda) discussing conventional use of alpha synuclein to generate antibodies for research purposes, and the '947 and '112 patents discussing adjuvants suitable for human administration. The case of obviousness is not simply a combination of two substances having a

common use from different lists but the replacement of what would have appeared to have been a more preferred adjuvant (Freund's adjuvant) for research purposes in animals with a less preferred substance as a result of which unexpectedly, the combination confers an improved suitability for human use. The issue is not whether the '947 and '112 patents teaching regarding adjuvants suitable for human administration constitutes prior art, but whether the claimed compositions would have been obvious in light of such teaching. In appellant's submission, this teaching only serves to reinforce the unexpected result discussed above; namely that the claimed compositions have an unexpectedly advantageous property relative to the art compositions of suitability for human administration. This property could not have been expected without knowledge that the claimed compositions had a therapeutic role in humans.

With respect to claim 54, the Examiner alleges that it would have been obvious for any researcher to follow GMP procedures as provided by the FDA for any composition expected to be used as a therapeutic drug (final office action at p. 4, last sentence). Appellant would agree to the extent that any therapeutic drug intended for human administration would be manufactured under GMP procedures. However, appellant's point is that the alpha-synuclein discussed by Ueda was not intended as drug for human administration but rather was a research reagent to generate antibodies for laboratory research.

8. CONCLUSION

For these reasons, it is respectfully submitted that the rejection should be reversed.

Respectfully submitted,

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9. CLAIMS APPENDIX

1. A composition comprising an agent effective to elicit an immunogenic response to alpha-synuclein and an adjuvant that is pharmaceutically acceptable for human administration, wherein the adjuvant is selected from the group consisting of QS21, monophosphoryl lipid, alum, CpG, GM-CSF and M-CSF, wherein the agent is alpha-synuclein or an immunogenic fragment thereof.

3. The composition of claim 1, wherein the agent is alpha-synuclein.

4. The composition of claim 1, wherein the agent is immunogenic alpha-synuclein fragment.

5. The composition of claim 4, wherein the agent is NAC.

6. The composition of any one of claims 1 or 3-5, wherein the agent is linked to a carrier molecule to form a conjugate.

54. The composition of claim 1, manufactured under good manufacturing practice conditions.

55. The composition of claim 1, wherein the agent is filter sterilized.

10. EVIDENCE APPENDIX

YOSHIMOTO et al., *Proc. Natl. Acad. Sci. USA* 92:9141-9145 (1995), cited by information disclosure statement filed November 01, 2007 as cite no. 176, entered by office action of January 08, 2008.

WAKABAYASHI et al., *Neuroscience Letters* 239(1):45-48 (1997), cited by examiner in office action of November 15, 2006.

CLELAND et al., *J. Pharm. Sci.* 85(1):22-28 (1996), cited by examiner in office action of November 15, 2006.

IWAI et al., *Neuron* 14:467-475 (1995), cited by information disclosure statement filed March 05, 2007 as cite no. AC, entered by office action of March 30, 2007.

HARLOW et al., *Antibodies, A Laboratory Manual* (1988). p. 98, cited by information disclosure statement filed March 05, 2007 as cite no. AB, entered by office action of March 30, 2007.

CHANG et al., *Advanced Drug Delivery Reviews* 32:173-186 (1998), cited by information disclosure statement filed March 05, 2007 as cite no. AA, entered by office action of March 30, 2007.

11. RELATED PROCEEDINGS APPENDIX

Copies of decisions in Appeal Number 2006-3375 are attached.